DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-662/S-044

Hoffmann-La Roche Inc.
Attention: Joanna Waugh, BSc., Hons,
Group Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, N. J. 07110

Dear Ms. Waugh:

Please refer to your supplemental new drug application dated September 17, 2001, received September 18, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accutane (isotretinoin) capsules, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated October 4, 8, 9 (2), and 25 (facsimile), 2001.

This supplemental new drug application provides for revisions to labeling to reflect the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Program, an enhanced risk management program to help prevent fetal exposure to Accutane. In addition, this application specifies several evaluation metrics including those related to 1) female participation in the Accutane Survey conducted by the Slone Epidemiology Unit of Boston University, and 2) prescriber and pharmacist compliance with the use of Accutane qualifying stickers.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert; patient *Informed Consent* forms; *Medication Guide*; booklet for prescribers entitled *System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Guide to Best Practices*; Prescriber Checklist; *S.M.A.R.T. Letter of Understanding for Prescribers; Accutane Qualification Sticker;* Pharmacist *Accutane Dispensing Guide*; Carton Dispensing Instructions; FDA Letter to Pharmacy Boards; *Dear Accutane Prescriber Letter*; *Dear Pharmacist Letter*; *Be Smart, Be Safe, Be Sure for Women; Be Smart, Be Safe, Be Sure for Men*; immediate container and carton labels).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved

supplement NDA 18-662/S-044." Approval of this submission by FDA is not required before the labeling is used.

The following are conditions for approval of this labeling supplement:

1. All of the components and tools associated with S.M.A.R.T. and/or described in the appended documents are conditions for approval. The only exceptions are the Continuing Medical Education seminar, the free urine pregnancy test kits, and the progress note pads for prescribers. We recognize the utility of these components, but consider them optional because, by definition, the prescriber commits to obtaining adequate training and patient pregnancy testing in order to receive the Qualification Stickers.

2. You should either place the *Medication Guide* into the unit packaging with implementation of S.M.A.R.T. or submit within 30 days an amended version (based on consumer comprehension testing). If the Medication Guide is not placed into the unit packaging now, you should submit, within one week, documentation that all retail outlets for Accutane, including legal on-line pharmacies, have been sent an adequate re-supply of Medication Guides.

3. A plan should be submitted within one week for ensuring, to the greatest practical extent, that all packages and documents in the marketplace are the new approved materials as soon as possible.

4. The adequacy of S.M.A.R.T will be a review issue for re-evaluation on a continuing basis. The Plan for a back-up program should include:

   - Mandatory registration of all patients both male and female receiving Accutane
   - Mandatory registration and certification of practitioners prescribing Accutane
   - Mandatory reporting of all fetal exposures to Accutane
   - Mandatory restricted distribution through registered pharmacies

   Please submit a detailed proposal for such a back-up plan by January 31, 2002.

5. Pharmacist *Accutane Dispensing Guide*:

   - The words “as required by law” should be added to the statement “Dispense an Accutane Medication Guide with each Accutane prescription, *as required by law”*.
   - Add the color of the Qualification Sticker (yellow) to the Guide.
   - The word “automatic” is not necessary in association with “refills”.

6. Bulk Carton Dispensing Instructions for Pharmacists: Ensure that the operational procedure for dispensing is printed on the “permanent” side of the carton, not the part that is torn off in opening. The *Procedure for Pharmacist* should include “No Refills”.

7. Produce a patient education video that directly and graphically links serious birth defects to Accutane exposure, similar to the video for thalidomide produced by Celgene. This should be submitted as a labeling supplement within 3 months.

8. Both of the *Informed Consent/Patient Agreements* must meet the requirements for Medication Guide

minimum font size.

9. For educational brochures (in addition to edits as shown in documents):

   - Remove all acne efficacy photographs
   - Insert, where appropriate, information about the newly approved hormonal contraceptive ring device
   - Add Table of Contents to the *Guide to Best Practices* and *Preventing Pregnancy: Guide to Contraception*
   - On the front of the patient guides (*Be Smart, Be Safe, Be Sure*), place a prominent space clearly indicating that the prescriber should write in the phone number that their patient should call if they have questions or problems on Accutane. This will help alleviate semantic confusion about who is the "doctor", the "provider", the "prescriber", etc.
   - *Be Smart, Be Safe, Be Sure* for men:
     - The cover should delete reference to pregnancy prevention and the logo for birth defects.
     - The Boxed Warning for women on the second page should be deleted.
     - The "Additional Information" for men should be presented before the "brochure" for all patients (*Important Information Concerning Your Treatment with Accutane*). The wording for "Additional Information" should be as appended (replace what was submitted).

10. Regarding the Prescription Compliance Survey:

    - For each survey wave, you should provide an assessment of the representativeness of the pharmacies surveyed compared with all dispensing pharmacies in the SK & A pharmacy universe. Pharmacy characteristics that are anticipated to affect compliance with the use of Accutane qualification stickers, and which should be critically evaluated, include store type, geographical region, population density served, and total prescription volume.

    - For each survey wave, you should expand the field audits that will be conducted to directly validate the accuracy with which Accutane prescriptions are collected and characterized by pharmacies. We recommend a 10% audit, at a minimum, of the completeness and accuracy of survey responses for each pharmacy stratum, as characterized by store type, geographical region, population density served, and total prescription volume.

    - You should clarify that pharmacists will report on sticker use for a month prior to recruitment in a survey, and that pharmacists who have declined to participate will not be recontacted.

11. Regarding the Accutane Survey (conducted by the Slone Epidemiology Unit):

    - A precise method for calculating enrollment in the Slone Survey must be specified. Methods for calculating both the numerator (respondents providing useful survey information) and the denominator (all female Accutane users in the U.S.) are necessary.

    - You are directed to seek a means of assessing representativeness of the Slone Survey that is better than the comparison of survey respondents to a managed care population (MCP), unless it can be documented that the MCP is nationally representative and reliably captures both

pregnancies and contraceptive practices/prescriptions. You should explore comparisons of demographic data obtained by linking census data to the zip codes of Accutane users and Slone Survey respondents.

- Since women may complete 2 or more versions of the DAT3 questionnaire, analyses of this survey wave should include subanalyses of women responding more than once and provide a clear *a priori* plan for handling conflicting data should they occur among multiple DAT3 responses by individual respondents.

12. The proposed Independent Chart Review is not acceptable.

13. You should submit a comprehensive report on the SMART Program, including information on the metrics achieved during the first full year of implementation of Qualification Stickers (April 10, 2002 through April 9, 2003), to FDA on or before June 30, 2003. FDA plans to convene a meeting with the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC), including, teratologists, women's health practitioners, dermatologists, pediatricians, and medical ethicists, to discuss survey findings and measures of the program's overall effectiveness. Changes to the S.M.A.R.T. program may be required, including a mandatory registry program.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA regarding post-marketing reporting of adverse drug experience set forth under 21 CFR 314.80 and 314.81. As indicated in the FDA letter of October 27, 2000, to meet your postmarketing reporting requirement under 21 CFR 314.80 (c) and 21 CFR 314.81 (b), you should submit the following:

- All pregnancy exposures, regardless of the outcomes, as serious, labeled event reports in your annual periodic report;

- A summary and discussion of the clinical significance of the pregnancy exposures in the same annual periodic report and

- All reports of fetal abnormalities as 15-day expedited reports.

In addition, you should include a status summary of each condition in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these conditions for approval must be prominently labeled.

You may request a meeting with the staff of the Office of Postmarketing Drug Risk Assessment to discuss the details of your responses to conditions 10 and 11 outlined in this letter.

If you have any questions, please call Indira Hills, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure